CASE REPORTS

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Parathyroid Carcinoma Causing Hyperparathyroidism

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IN a review of the 322 cases of parathyroid adenoma reported up to 1945 it is stated that multiple tumors were described in 20 instances.[2] The reviewers point out, however, that only two of the 20 cases were reported after 1938, the year in which Albright's paper on secondary hyperplasia of the parathyroids appeared. Hence, it would appear that multiple true adenomas of the parathyroids are rare.

Malignant adenomas of the parathyroids *causing hyperparathyroidism* are considered very rare by most authors. Alexander[1] and his coworkers were able to find only seven reports of such cases in their review. These reviewers, however, appended reports of 14 new cases of hyperparathyroidism, with the opinion that the adenoma in 13 of the cases was malignant. Criteria of malignancy were invasion of capsule or blood vessels, or, in some cases, merely certain cytologic features. Metastasis was not demonstrated in any of the 13 cases, and in the seven reviewed reports metastasis was described in only one instance. It would seem that classification of parathyroid tumors as benign or malignant has depended largely on debatable criteria of malignancy.

REPORT OF CASE

The patient, a 51-year-old Caucasian female, was first seen at St. Luke's Hospital in December, 1945. For two years she had experienced pain on movement of various joints. During the past year she had become very weak and had lost 24 pounds of weight. Vomiting had occurred during the last three months. Polyuria had been present for an unknown period of time. Incidental to an unrelated episode, asymptomatic calculi were demonstrated in the region of each kidney by roentgen examination in 1927.

Physical examination revealed a weak, ill woman with flaccid muscles. A mass was palpable in the region of the right lobe of the thyroid. The blood pressure was 142 mm. systolic and 82 mm. diastolic.

Laboratory studies demonstrated 10 gm. of hemoglobin per 100 cc. of blood, 3.8 million erythrocytes and 8,800 leukocytes per cubic mm. (the differential count of leukocytes was normal). The urine exhibited a specific gravity of 1.005. It contained 100 mg. of protein per 100 cc., and a large amount of calcium was demonstrated by the Sulkowitch test. Bence-Jones protein was not present. Microscopic examination revealed a few leukocytes and an occasional granular cast. Serum calcium was 18.5 mg., phosphorus 5.0 mg. per 100 cc. Alkaline phosphatase was 17.8 Bodansky units, acid phosphatase 1.5 units. Albumin was 3.4 gm., globulin 2.7 gm. per 100 cc. of serum. The non-protein nitrogen content was 54 mg. per 100 cc. of blood.

X-ray examination revealed generalized osteoporosis. In addition, there were cystic areas in ribs, cranium, vertebrae and long bones; some cystic lesions were apparently expansile. A rib fracture was demonstrated, as well as collapse of a vertebral body. Small calculi were seen in the region of each kidney. Diffuse renal calcification was not demonstrable.

Sternal puncture and rib biopsy were carried out. Exploration of the neck was performed Dec. 31, 1945. Two tumors were found. The smaller was encapsulated and located a few millimeters from the inferior border of the right lobe of the thyroid, from which the tumor was distinct. The larger tumor was incorporated within the right lobe of the thyroid, and was thought to be a thyroid adenoma until rapid microscopic examination revealed its nature. Both tumors were extirpated.

On the day following operation the blood calcium had dropped to 11.0 mg. per 100 cc. of serum. On Jan. 3 the calcium level was 9.0 mg., numbness of the mouth developed, and Chvostek's sign could be elicited. Despite continuous calcium therapy, the blood calcium dropped to as low as 7.3 mg. The level then quickly became and remained normal. Postoperative Sulkowitch tests of the urine revealed no abnormal amount of calcium.

The patient then returned to her family physician in another city, where she improved and x-rays demonstrated complete healing of bone lesions. She returned to St. Luke's Hospital Feb. 18, 1947, because of recurrence of former symptoms. The calcium level was found to be 13.3 mg. per 100 cc. of serum, phosphorus 2.3 mg. Roentgen examination revealed demineralization of the calvarium, without cystic areas. The ribs appeared normal, a new cystic lesion of a tibia had appeared, and the renal calculi were still present. Studies were interrupted by departure of the patient for treatment elsewhere.

TISSUE EXAMINATION

The rib biopsy specimen consisted of a little reddish tissue exhibiting no evidence of brownish color to gross examination. Microscopically, the typical picture of giant cell tumor was presented. Very little hemosiderin was apparent. The sternal puncture films contained very few cells other than non-nucleated erythrocytes. A few cells were relatively plump spindle-shaped forms with a vesicular, elongated nucleus. These conformed to the spindle cells found in sections of the giant cell tumor from the rib.

The smaller parathyroid tumor was 15x18x8 mm. in size. The smooth surface was completely encapsulated, and the bulging cut surface revealed a soft, tan, homogeneous tissue. The larger mass was 28x26x18 mm. in size, and was encapsulated except over a small area where it had been fused to a little thyroid tissue. Sections revealed a pinkish-gray tissue traversed by narrow and broad bands of firm white tissue.

Microscopically, the two tumors were similar. They were undoubtedly of parathyroid origin. There were masses and anastomosing columns of large polygonal and columnar cells (see Figures 1 and 2). Most of the cells were of the "chief cell" variety, with foamy cytoplasm. A moderate number were of "water clear" type, and a few oxyphil cells were present. The cells were much larger than normal, and many presented a very large nucleus with one or two very prominent nucleoli. An occasional mitotic figure was seen. The stroma was scant, save for areas of fibrosis in the larger tumor. The

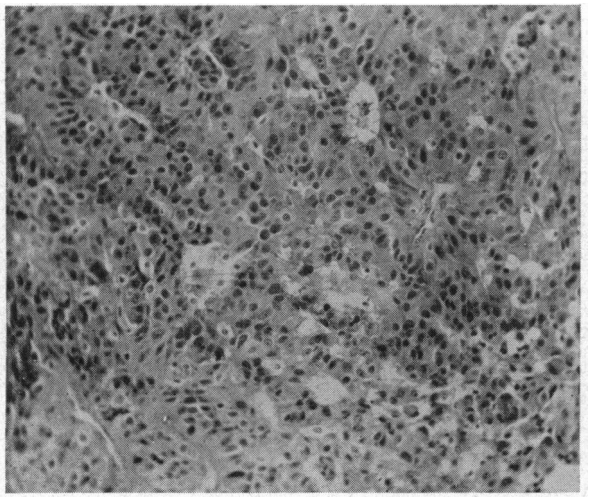

Figure 1.—Magnified 130 times.

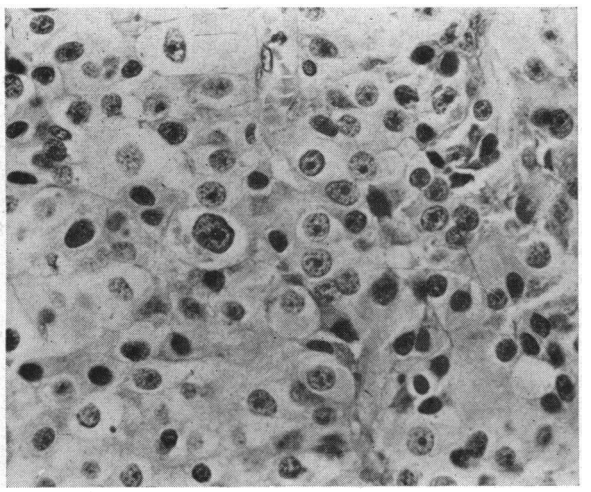

Figure 2.—Magnified 440 times.

latter tumor presented invasion of thyroid tissue and growth into the lumen of venules (see Figure 3). A small separate fragment of tissue removed during the surgical operation consisted of apparently normal thymic tissue enclosing a small amount of parathyroid tissue; the latter appeared normal.

ANIMAL INOCULATION

Extracts* of each tumor were injected intravenously into rabbits. The calcium level of each animal rose to an average value of 19 mg. per 100 cc. of serum, from a pre-injection level of 12 mg. The experiment was controlled by injection of other rabbits with various tissues.

DISCUSSION

The histologic features of the parathyroid tumors in the case reported were those commonly accepted as being indicative of malignancy. In view, however, of the fact that only one case of metastasis from a malignant adenoma of the parathyroid *with hyperparathyroidism* has been reported, a circumspect attitude in the diagnosis of "malignancy" would seem desirable. One might consider, in the present case, that the tumors represent multicentric origin or, on the other hand, malignant extension. According to either interpretation, this case presents a rare situation. Investigation of the recurrence of hyperparathyroidism in the patient was aborted by her decision to seek treatment elsewhere. A preliminary part of the investigation was to have been biopsy of the new tibial lesion to determine if it represented metastasis of parathyroid tissue, or merely another giant cell tumor.

*Method of Collip, as described in Physiol. Basis of Med. Pract., Best & Taylor, 3rd ed., p. 1185.

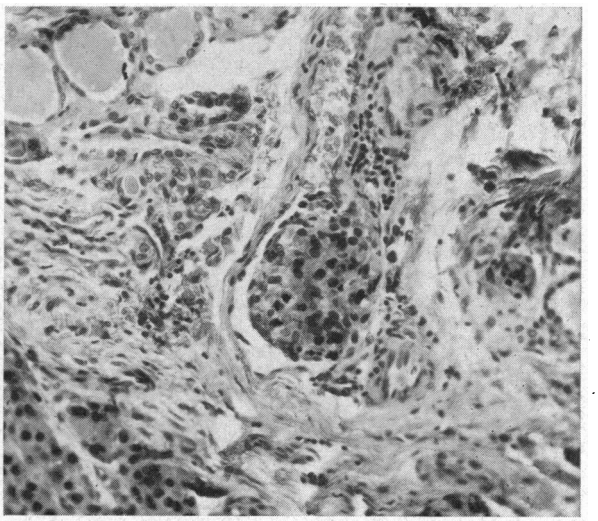

Figure 3.—Magnified 160 times.

SUMMARY

Extirpation of two parathyroid tumors was followed by temporary disappearance of hypercalcemia and bone lesions. Extracts of the tumors produced hypercalcemia in animals. The tissue findings are discussed, particularly in regard to possible malignancy of the adenomas.

Note: The author is indebted to the patient's physicians, Dr. P. A. Taylor and Dr. A. R. Kilgore, for permission to present the pathologic features of this case.

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Addendum: The above paper is reproduced as presented before the pathology section of the California Medical Association under the title "Hyperparathyroidism, Report of a Case Presenting Two Parathyroid Adenomas, Possibly Malignant." Subsequently it was learned that later in May, 1947, operation at the Mayo Clinic revealed local recurrence of tumor and metastases to right lower deep jugular lymph nodes. In both locations the tumor was identical in microscopic appearance to that found at the original operation. The blood calcium level was 17 mg. per cent just before the second operation, then fell to normal postoperatively. The case is still under investigation.

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Discussion by E. M. HALL, M.D.

I concur in the diagnosis of "malignant adenoma of the parathyroid" as presented by Dr. Dorgeloh. Well-substantiated malignancies of the parathyroid glands are rare, but this invades the thyroid gland and at least one of the blood vessels, thus setting the stage for metastasis.

A similar tumor was reported by Hall and Chaffin in 1934. A 46-year-old white male had a mass the size of his fist removed from the left side of his neck in March, 1931. The mass was of liver-like consistency except for one part that was cystic. The diagnosis made by another pathologist was "adenoma of the parathyroid and cyst adenoma of the

thyroid gland." The blood calcium was 9.9 mg. per cent and no changes were demonstrated in the bones by x-ray examination. The patient returned to the hospital in November, 1932, with several small recurrent nodules in or near the operative scar. They ranged from 1 to 1.5 cm. in diameter, some of them definitely invading muscle. Microscopic examination revealed not only invasion of skeletal muscle but also a mass of tumor cells within a small blood vessel in the fibrous capsule. Blood calcium and phosphorus determinations were within normal limits. The bones appeared normal in the roentgenogram. The patient was able to return to work and remained well until late in December, 1936. Weakness, night sweats and loss of weight disturbed him during the early weeks of 1937. He developed fever and pain in the chest, and pneumonia was diagnosed. The fever and pain lasted for some three months. By September, when the patient entered the Los Angeles County General Hospital, he had lost 50 pounds in weight. Roentgen examination showed the right lung field almost completely filled with a hazy homogenous density.

The patient died in September, 1938. At autopsy massive tumor metastases were shown to have replaced most of the right lung, and a 3 cm. nodule was present in the lymph nodes at the hilum. Microscopic examination revealed a picture very similar to the tumor seen previously. Here, then, is an instance in which neoplasm similar in cell pattern and in invasive properties to the one reported by Dr. Dorgeloh, finally produced metastases to the lung with fatal outcome. It was four years from the time of the second operation to the onset of symptoms.

It is interesting that bony changes including cystic areas and benign giant cell tumors were present in Dr. Dorgeloh's patient. Of the 20 parathyroid malignancies reported to 1940 only about one in four revealed bone destruction and high serum calcium levels. In a recent report by Alexander, Broders, et al (1944) 12 out of 13 adenomas of the parathyroids reported were considered Grade I adenocarcinomas. It is evident that a less rigid standard is used in classifying this group since malignancy was judged on a basis of cellular anaplasia while no invasion of surrounding tissues or blood vessels was present except in one case.

REFERENCES

1. Alexander, et al: Am. J. Surg., 65:157, 1944.
2. Norris: International Abstracts of Surgery, 84:1 (Jan.), 1947.

Severe Stomatitis Due to Erythema Multiforme — Its Differentiation from Human Foot and Mouth Disease

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BECAUSE of its varied and protean clinical manifestations, erythema multiforme is of general medical interest. The disease was first recognized in 1817 by Bateman and Bulkley, in 1846, reported the first American cases as "Herpes Iris." Hebra,[3] in 1866, fully described the morphologic features of the eruption under the term "erythema exsudativum multiforme." Hebra was among the first investigators to recognize erythema multiforme to be of internal or systemic origin and not local in causation. Quinquaud ranks priority in describing the mouth lesions in vesiculobullous erythema multiforme. The implication of the viscera in the etiology of erythema multiforme was stressed at the beginning of this century by Osler,[8] who called the internal features of the disease to the attention of the medical world.

Erythema multiforme (Hebra) is essentially cutaneous in location and oral mucosal involvement is present in about 25 per cent of the cases. Rarely, the mucosae of the eyes, nose, esophagus, labia minora, preputium, glans penis, urethra, vaginal tract, cervix and anus are involved.

The association in erythema multiforme, however, of severe vesiculobullous oral mucosal lesions with a paucity of cutaneous lesions has produced confusing and bizarre clinical pictures. In some instances, severe mucous membrane involvement has occurred with entire absence of a skin eruption.[1] Some investigators have described these unusual mucous membrane manifestations of erythema multiforme as new diseases. Thus Rendu, in 1916, termed a severe bullous stomatitis associated with similar lesions on the conjunctival, anal, and penile mucous membranes and a cutaneous vesicular eruption, "Ectodermose Erosive Pluriorificielle." Baader, in 1925, named severe erythema multiforme of the oral cavity associated with cutaneous lesions, "Dermatostomatitis." Stevens and Johnson,[10] in 1922, reported erythema multiforme with predominant involvement of the oral and conjunctival mucous membranes as "a new eruptive fever associated with stomatitis and ophthalmia." This syndrome has also been referred to in the medical literature as "Stevens-Johnson disease." In the erythema multiforme group may also belong the "triple syndrome complex" of Behcet consisting of ulcerations of the oral and genital mucous membranes associated with retinitis and iridocyclitis.

When erythema multiforme is associated with stomatitis, fever, malaise and vesicular lesions on the hands and feet, a clinical picture is produced that resembles foot and mouth disease in man. If this clinical picture occurs in a resident of a dairying or livestock-raising area such as California, where foot and mouth disease epidemics in animals occurred in 1914, 1924, and 1929,[7] it can easily lead to an unwarranted diagnosis of the human form of foot and mouth disease when the clinical diagnosis is unsupported by confirmatory laboratory tests. This close clinical resemblance between erythema multiforme and the human form of foot and mouth disease has been stressed by Klauder[4] and Lever. Internists, pediatricians, ophthalmologists, and dermatologists may especially be called in consultation in cases of erythema multiforme, the choice of consultant depending on the location of the mucous membranes attacked and the constitutional or systemic manifestations predominant. It is the purpose of this article to report a case of severe stomatitis due to erythema multiforme resembling the human form of foot and mouth disease and to differentiate this type of stomatitis from important simulating mouth eruptions.

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